REMARKS

Applicant thanks the examiner for carefully reviewing the application. Please reconsider this application in view of the above amendments and the following remarks.

Disposition of the Claims

Claims 1-9, 37-40, 43-44, 49 and 50 are pending after the restriction requirement.

Claim Amendments

Claims 1, 2, and 37-40 have been amended to delete non-elected subject matter, without disclaimer or prejudice. Applicant reserves to right to prosecute the non-elected subject matter in one or more divisional applications. No new matter is introduced by way of this amendment.

Claim Objection

Claims 1, 37, and 38 were objected to for containing non-elected subject matter. Claims 1-2 and 37-40 have been amended to delete the non-elected subject matters. Accordingly, withdrawal of this rejection is respectfully requested.

Claim Rejections under 35 U.S.C. § 112

Claims 1-9 and 49 were rejected under 35 U.S.C. § 112, ¶ 1, for failing to comply with the enablement requirement. The examiner asserts that applicant has not enabled the treatments of any diseases associated with inhibition of human stearoyl-CoA desaturase (hSCD). This rejection is respectfully traversed.

Legal standard

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde,* 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). *See also*, M.P.E.P. § 2164.01

The Specification (Example 6) teaches an *in vitro* assay for testing the claimed compounds' ability to inhibit stearoyl-CoA desaturase-1 activity. The assay is also known in the art, see e.g., PCT publication No. WO 2001/062954. The Declaration under 37 C.F.R. 1.132 filed herewith attests to the fact that one skilled in the art would not have any difficulty in preparing or testing these compounds. In view of the state of the art at the time the instant application was filed (see discussion below), one skilled in the art would know how to assay these compounds for SCD inhibition and would reasonably expect that the compounds of the invention would be useful in treating diseases mediated by SCD, including type II diabetes, obesity, dyslipidemia, metabolic syndrome and acne in humans.

In one aspect, Applicants respectfully submit that one skilled in the art would reasonably expect that the compounds of the invention would be useful in treating type II diabetes by virtue of their ability to inhibit stearoyl-CoA desaturase activity. It is a well-known fact that patients with type II diabetes produce insulin, but lose the ability to respond to insulin signaling, i.e., the patients have decreased insulin sensitivity. Through the inhibition of stearoyl-CoA desaturase-1 activity, one can increase insulin sensitivity, thereby preventing or treating Type II diabetes. In Ntambi J.M. *et al., Proc. Natl. Acad. Sci.*, (August 20, 2002), Vol. 99, No. 17, pp. 11482-6, it was shown that mice with disrupted stearoyl-CoA desaturase-1 activity have increased insulin sensitivity (see first paragraph, pp. 11482). Moreover, it was shown (on page 11484) that stearoyl-CoA desaturase-1 knock-out mice showed improved glucose tolerance and a greater response to glucose lowering effect of insulin when compared to wild-type mice. The data

supports the conclusion that inhibition of stearoyl-CoA desaturase-1 activity would lead to increased insulin sensitivity, which is a desired endpoint for the treatment of Type II diabetes. Thus, Applicants respectfully submit that the instant application is enabling for the use of the compounds in treating humans for type II diabetes and/or for increasing insulin sensitivity.

In addition, Applicants respectfully submit that it is possible to treat obesity by inhibiting stearoyl-CoA desaturase-1 activity. As noted in Park, E.I. *et al., J. Nutr.* (1997), Vol. 127, pp. 566-573 (submitted herewith), mice provided with a diet that lowered the expression of stearoyl-CoA desaturase-1 had lower body weight and lower serum concentrations of total cholesterol, triglycerides, and HDL cholesterol. Furthermore, Ntambi *et al*, cited above, demonstrated that loss of stearoyl stearoyl-CoA desaturase-1 function (activity) protected mice from gaining weight from a high-fat diet. Thus, one skilled in the art, in view of these references, would reasonably expect the compounds of the invention, by virtue of their ability to inhibit stearoyl-CoA desaturase-1 activity, to be useful in treating obesity in humans based on the disclosure of the Specification and the IC_{50} data.

With respect to treating dyslipidemia and lowering triglyceride, LDL and VLDL serum levels, WO 2001/062954 disclosed an animal model for testing the claimed compounds' effectiveness in lowering triglyceride, LDL and VLDL serum levels (see Example 1) and demonstrated the correlation between stearoyl-CoA desaturase-1 activity in humans and levels of serum triglycerides (see Example 2). Furthermore, as noted by Miyazaki, M. *et al., Journal of Lipid Research* (2001), Vol. 42, pp. 1018-1024 (submitted herewith), triglyceride synthesis was dramatically reduced in the liver of SCD -/- mice fed a lipogenic diet compared to normal mice. See also Miyazaki, M. *et al., J. Biol. Chem.* (2000), Vol. 275, No. 39, pp. 30132-30138 (submitted herewith). These observations demonstrated that the induction of triglyceride synthesis is highly dependent upon the expression of the stearoyl-CoA desaturase-1 gene. Thus, one skilled in the art, having knowledge of WO 2001/062954, the Miyazki references, the instant Specification and the IC_{50} data of the claimed compounds, would reasonably expect the compounds of the invention to be useful in lowering triglyceride, LDL, and VLDL serum levels and treating dyslipidemia in a human subject. Furthermore, as noted in Attie, A.D. *et al., Journal of Lipid Research* (2002), Vol. 43, pp. 1899-1907, which was published on August 16,

2002, stearoyl CoA desaturase activity was hypothesized as rate-limiting in triglyceride production in a wide array of dyslipidemias.

Furthermore, Applicants respectfully submit that it is possible to treat acne by inhibiting stearoyl-CoA desautrase-1 activity. Zheng *et al.*, *Nat. Genet.* (1999) 23:268-270 (submitted herewith), showed that rodents lacking a functional SCD1 gene had changes to the condition of their eyes, skin and coat thereby reducing the excessive sebum production that typically results in the formation of acne. As noted by Miyazaki *et al.*, J. Nutr. (2001), Vol. 131, pp 2260-68 (submitted herewith), SCD1-/- mice developed cutaneous abnormalities and atrophic sebaceous and meibomian glands compared to normal mice. These observations demonstrated that reduction of the sebum production can be effected by the inhibition of SCD1 and one skilled in the art would reasonably expect the compounds of the invention, by virtue of their ability to inihibit stearoyl-CoA desaturase-1 activity, to be useful in treating acne in humans.

Therefore, in view of the foregoing remarks, the Applicant respectfully submits that the Specification, in view of the existing knowledge in the prior art, is clearly enabling for methods of treating disease mediated by SCD, including type II diabetes, obesity, dyslipidemia, metabolic syndrome and acne by the administration of a compound of the invention to the human.

The following specifically addresses the points raised by the Examiner:

(1) Nature of the Invention and (2) Breadth of the claims

As noted above, SCD inhibitors have been known to be effective in treating various diseases or conditions mediated by SCD. This invention relates to new compounds as inhibitors of SCD. Applicant respectfully notes that methodology for the synthesis of these compounds is clearly described and is well within the skills of an ordinary artisan.

(3) State of the Prior Art and (4) the Predictability or Unpredictability of the Art

The Examiner cites Browlie et al. (WO 01/620954, p. 3, lines 7-27) as teaching that inhibition of hSCD does not have any biological effect. Actually, the cited reference teaches the opposite to what is asserted by the Examiner.

The section in Browlie et al. cited by the Examiner is the background section of that application. In this background section, the inventors described the state of the art prior to their invention in order to bring out the importance of their invention. The cited prior art references in this background section were published in 1992 and 1997.

Browlie et al. actually show the link between hSCD and various human disorders. "In particular, SCDl biological activity in humans is directly related to serum levels of triglycerides and VLDL. In addition, SCDl biological activity also affects serum levels of HDL, LDL, and/or total cholesterol, reverse cholesterol transport, and the production of secretions from mucous membranes, monounsaturated fatty acids, wax esters, and/or the like." (p. 5, lines 7-13).

They further teach that "agent which modulates the biological activity of said human stearoyl-CoA desaturase (hSCD1) and is useful in treating a human disorder or condition relating to serum levels of triglyceride or VLDL." (p. 5, lines 17-19).

Contrary to Examiner's assertion, this reference clearly shows that hSCD is linked to several human disorders and conditions, and that agents that can modulate hSCD activity are useful in treating these conditions.

This reference, together with many other prior art references, including those discussed above, clearly established the link between hSCD and the various disorders described in the present invention. More importantly, these references show that inhibition of SCD can be effective in controlling these conditions.

Based on this prior art knowledge, one interested in finding useful agents to treat hSCD-mediated disorders would only need to find out how to synthesize the

candidate inhibitors and how to perform SCD inhibition assays. How to assay for SCD inhibitors is taught in the prior art (e.g., Brownlie et al.) and clearly described in the specification of the present application. The Declaration under 37 C.F.R. 1.132 filed herewith attests to the fact that one skilled in the art would not have any difficulty in preparing or testing these compounds.

How to prepare compounds of the invention is also well described in the specification. As shown in Reaction Schemes 1-11 and various examples shown, the claimed compounds can be prepared by selecting properly protected starting materials or intermediates and reacting them according to the Reaction Schemes shown. Note that most of these reactions are common organic reactions. One of ordinary skilled in the art would not have to perform undue experimentations to obtain these compounds.

(5) The relative skill of those in the art

As noted by the examiner, the relative skill is high and one skilled in the art would not have any problem to duplicate the assay depicted in example 6. Applicant further submits that based on the detailed description, one skilled in the art would not have problem to prepare the compounds of the invention, either. The Declaration under 37 C.F.R. 1.132 filed herewith attests to the fact that one skilled in the art would not have any difficulty in preparing or testing these compounds.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples

The Examiner asserts that the specification does not provide guidance that inhibition of hSCD has any biological effect. As noted above, the Examiner's reliance on the background section of Brownlie et al. is misplaced. The prior art clearly supports the link between hSCD and the disorders described, and the prior art further shows that inhibitors of hSCD are useful in treating these disorders.

Because prior art clearly provides the link between hSCD inhibition and the treatments of the disorders, the only guidance needed to enable one skilled in the art

to practice the present invention relates to how to obtain the new SCD inhibitors claimed in the present invention. In that regard, there is plenty of guidance in the specification.

For reasons set forth above, Applicant respectfully submits that the specification is sufficient to enable one skilled in the art to practice the invention.

Double Patenting

Claims 1-9, 37-40, 43-44, and 49-50 are provisionally rejected on the ground of obviousness type double patenting as being unpatentable over claims 1-9, 35-39, and 42-43 of co-pending application No. 10/566,857 (Pub No. 2006/0293308). Claims 1-9, 37-40, 43-44, and 49-50 are provisionally rejected on the ground of obviousness type double patenting as being unpatentable over claims 1-9, 38,40, 41, and 43-45 of co-pending application No. 10/567,009 (Pub No. 2006/0252767).

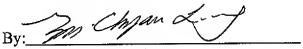
A terminal disclaimer is filed herewith. Accordingly, withdrawal of this rejection is respectfully requested.

Conclusion

Applicant believes this reply is fully responsive to all outstanding issues and places this application in condition for allowance. If this belief is incorrect, or other issues arise, the Examiner is encouraged to contact the undersigned or his associates at the telephone number listed below. Please apply any charges not covered, or any credits, to Deposit Account 50-0591, Reference 17243/003001.

Dated: August 29, 2008

Respectfully submitted,

By: 

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